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Guidance for Industry

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

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REVISED

GUIDANCE[1]

DICLOFENAC SODIUM TABLETS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION TESTING

I. INTRODUCTION

A. Clinical Usage/Pharmacology

Diclofenac sodium (DS) is an orally administered nonsteroidal antiinflammatory drug (NSAID), which also has analgesic and antipyretic properties. Currently approved indications (1) for DS are for the acute or chronic treatment of the signs and symptoms of rheumatoid arthritis (RA), osteoarthritis, and ankylosing spondylitis. Doses above 200 mg/day in 3-4 divided doses have not been studied in RA patients. Diclofenac sodium inhibits prostaglandin synthesis, an action which may be associated with its mechanism of action. Due to possible cross-reactivity, DS is contraindicated in patients in whom aspirin or other NSAID has produced asthma, urticaria, or other allergic reactions.

Diclofenac sodium is currently marketed as Voltaren® (Geigy) as 25, 50, and 75 mg enteric-coated (EC) tablets (NDA #19-201 approved 7/28/88).

B. Chemistry

Diclofenac sodium is 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid monosodium salt and has a pKa of 4.0 (1-2).

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[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-594-2290; Fax: 301-594-0181).

C. **Pharmacokinetics**

Diclofenac sodium is rapidly absorbed following oral administration with reported time of maximum concentration (T_{MAX}) mean values of 1-3 hr (1-5) and ranges of 1-5 hr (6-9) under fasting conditions in normal volunteers. After single oral doses of 25, 50, and 75 mg EC tablets, reported maximum concentrations (C_{MAX}) in normal fasting subjects were 0.5-1 (1-2), 0.9-1.5 (1,2,4,5), and 1.9-2 (1,4,5) μg/ml, respectively. Area under the plasma concentration-time curve (AUC) increases linearly over the dose range 25-150 mg (1,4,5); however, C_{MAX} is less than dose-proportional with values of 1, 1.5, and 2 μg/ml after doses of 25, 50, and 75 mg, respectively (1). Diclofenac sodium undergoes first-pass metabolism with a systemic availability of 50-60% (1-5). Food may markedly delay the rate of absorption from EC tablets but does not appear to significantly change AUC (1,3-5,10). In two single dose (50 mg) studies (10), the nonfasting mean T_{MAX} values were 5.4 hr (N = 12, range 2.5-12 hr) and 9.7 hr (N = 6, range 8-10 hr). The volume of distribution (Vd) of DS is about 0.12-0.17 L/kg (3-5). The drug is ≥ 99% bound to plasma proteins (albumin) (1-5). After an IV dose, elimination of DS from plasma appears triphasic (11); after oral dosing, reported terminal ß-phase half-life (t½) values are 1-2 hr (1-5) with a range of 0.5-4.3 hr (6-9). The apparent elimination t½ of total radiolabelled compounds in patients with normal renal function is 25-33 hr (4,12).

The major route of elimination is hepatic clearance, with 90% of a dose eliminated in 96 hr (2,4). Approximately 65% of the dose is excreted in urine and the remainder is excreted in bile (1,2). The dose is excreted as glucuronide and sulfate conjugates of unchanged drug and four metabolites. The principal metabolite (4'-hydroxy) has about 1/40 the activity of the parent drug in animal models of arthritis (13,14). Because it accounts for 30-40% of the dose in man (2,14), this metabolite may contribute to the overall activity of DS.

II. **IN VIVO BIOEQUIVALENCE STUDIES**[2]

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[2] The sponsoring firm is advised that an Investigational New Drug Application (IND) filing may be required if dosing levels exceed those recommended in official labeling. Please refer to 21 CFR 312.2, 320.31(b)(1) and also Office of Generic Drugs Policy and Procedure Guide #36-92, Submission of an "Investigational New Drug Application" to the Office of Generic Drugs, issued October 13, 1992.

A. Product Information

1. FDA Designated Reference Product: Voltaren® 75-, 50-, or 25-mg delayed release oral tablets (Geigy)

2. Batch size: The test batch or lot must be manufactured under production conditions and must be of a size at least 10% that of the largest lot planned for full production or a minimum of 100,000 units, whichever is larger.

3. Potency: The assayed potency of the reference product should not differ from that of the test product by more than 5%.

B. Types of Studies Required

1. A single-dose, randomized, fasting, two-period, two-treatment, two-sequence crossover study comparing equal doses of the test and reference products.

2. A single-dose, randomized, three-treatment, three-period, six-sequence crossover, limited food effects study comparing equal doses of the test and reference products when administered immediately following a standard breakfast.

3. Per requirements stated in 21 CFR 320.22(d)(2)(iv), no waiver may be granted for the 25 or 50 mg strengths based on the 75 mg strength. Separate fasting studies must be performed for all of the strengths.

C. Recommended Protocol for Conducting a Fasted Single Dose Bioequivalence Study

Objective: To compare the rate and extent of absorption of a generic formulation with that of a reference formulation when given as equal labeled doses.

Design: The study design is a single dose, two-treatment, two-period, two-sequence crossover with a two week washout period between Phase I and Phase II dosing. Equal numbers of subjects should be randomly assigned to the two possible dosing sequences. Before the study begins, the proposed protocols should be approved by an institutional review board.

Facilities: The clinical and analytical laboratories used for the study should be identified along with the names, titles, and curriculum vitae of the medical and scientific/analytical directors.

Selection of Subjects: The sponsor should enroll a number of subjects sufficient to ensure adequate statistical results. It is recommended that a minimum of 36 subjects be used in this study. Subjects should be healthy volunteers aged 18 to 50 years and within 10% of ideal body weight for height and build (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Subjects should be selected on the basis of acceptable medical history, physical examination, and clinical testing. Subjects with any current or past medical condition which might significantly affect their pharmacokinetic or pharmacodynamic response to the administered drug should be excluded from the study. If female subjects are selected, the IRB should assure that appropriate safeguards (e.g., a pregnancy test) have been included in the study protocol. Written, informed consent must be obtained from all study participants before they are accepted into the studies.

Procedures: Following an overnight fast of at least 10 hours, subjects should be administered a single dose of the test or reference product with 240 mL of water.

Restrictions: Study volunteers should be subject to the following restrictions:

a. Water may be allowed except for one hour before and after drug administration when no liquid should be permitted other than that needed for drug dosing.

b. Subjects should fast for at least four hours after administration of the test or reference treatment. All meals should be standardized during the study.

c. No alcohol or xanthine-containing foods or beverages should be consumed for 48 hours prior to dosing and until after the last blood sample is collected.

d. Subjects should take no Rx medications beginning two weeks and no OTC medications beginning one week before drug administration and until after the study is completed.

Blood Sampling: For the fasting condition, venous blood samples should be collected pre-dose (0 hr) and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 5, 6, 8, 10, and 12 hr post-dose. Plasma/serum should be separated promptly and immediately frozen until assayed. Following a two week washout period, subjects should begin the second phase of the study.

Analytical Methods: Diclofenac should be assayed using a suitable method fully validated with respect to adequate sensitivity, specificity, linearity, recovery,

and accuracy and precision (both within and between days). Stability of the samples under frozen conditions, at room temperature, and during freeze-thaw cycles, if appropriate, should be determined. Chromatograms of the analysis of the unknown samples, including all associated standard curve and Q.C. chromatograms, should be submitted for one-fifth of the subjects, chosen at random. The sponsor should justify the rejection of any analytical data and provide a rationale for selection of the reported values.

Statistical Analysis of Pharmacokinetic Data (Blood Plasma/Serum): See Division of Bioequivalence Guidance, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design." In addition, the following parameters should be tabulated: lag time (TLAG), the time of the last zero concentration before the first nonzero concentration; and, adjusted TMAX (TMAXADJ), which is the observed TMAX minus TLAG.

Clinical Report and Adverse Reactions: Subject medical histories, physical examination reports and all incidents of possible adverse reactions to the study formulations should be reported.

D. Limited Food Effects Study

The labeling (1) for Voltaren® states: "The extent of absorption of Voltaren is not significantly affected when the drug is taken with food; however, there is usually a delay in the onset of absorption of 1 to 4.5 hours, with delays as long as 10 hours in some patients. There is also a reduction in peak plasma levels." For NSAID's such as diclofenac sodium, physicians generally prescribe the drug to be taken with meals and for pharmacists to dispense the drug with an auxiliary label "take with food."

In view of the wide range of reported values for T_{MAX} in the presence of food, it is recommended that the sponsor perform a pilot study to determine appropriate sampling times for the limited food effects study.

The limited food effects study should be performed in the same manner as the single-dose fasted study, with the following exceptions:

Procedures: Equal numbers of subjects should be assigned to each of the six dosing sequences possible in a three-treatment, three-period study design. Each subject will receive the following treatments:

Treatment 1: Generic Product, 75 mg, administered after

standard breakfast[3]

Treatment 2: Reference (Voltaren®, Geigy) Product, 75 mg, administered after standard breakfast

Treatment 3: Generic Product, 75 mg, dosed fasted

Following a ten hour fast, the subjects receiving the fed treatments should be served a standard breakfast (for example, begin meal at 0730). The subjects should have thirty minutes to finish the entire breakfast (finish entire meal by 0800), then be immediately dosed (exactly at 0800) with Treatment 1 or 2, above, taken with 240 mL of water. Subjects receiving the fasted treatment should be dosed with Treatment 3, taken with 240 mL of water only. The same lots of the test and reference products should be used as in the fasted study, above. No other food should be allowed for at least 4 hours post-dose with water allowed after the first hour. Subjects should be served scheduled standardized meals throughout the study.

The limited food study requirement for the 50 and 25 mg strengths of the generic diclofenac sodium product may be waived if: 1) the limited food study for the 75 mg strength demonstrates bioequivalence to the reference product; 2) the formulations for the 50 and 25 mg strengths are proportionally similar to the 75 mg strength.

Statistical Analysis: In general, a comparable food effect will be assumed provided the AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} mean values for the test product differ no more than 20% from the respective mean values obtained for the reference product in this study.

III. IN VITRO TESTING REQUIREMENTS

A. Dissolution Testing

The sponsor should conduct dissolution testing on 12 dosage units of the test product versus 12 units of the

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[3] Thirty minutes before dosing, each subject should be served a standardized, high fat content meal consisting of:

One buttered English Muffin
One fried egg
One slice of American cheese
One slice of Canadian bacon
One serving of hash brown potatoes
Eight fluid oz. (240 mL) of whole milk
Six fluid oz. (180 mL) of orange juice

reference product. The biostudy lots should be used for those product strengths tested in vivo. The following method and tolerances are recommended until an official USP method is adopted:

Apparatus:	USP XXII paddle
RPM:	50
Medium:	0.1 N HCl (120')
	sodium phosphate buffer[4] pH 6.8 (60')
Volume:	900 mL (acidic stage)
	900 mL (buffer stage)
Sampling Times:	acidic stage: 30, 60, 120 min
	buffer stage: 5, 10, 20, 30, 45, and 60 min
Tolerance (Q):	NMT 10% / 120 min (acidic stage)
	NLT 75% / 45 min (buffer stage)
Analytical:	As per USP XXII, if available, or other validated method

The percent of label claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

B. Content Uniformity Test

Content uniformity testing on the test product lots should be performed as described in USP XXII.

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[4] Prepare as described in reference 15.

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